ADVERSE DRUG REACTIONS

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INTRODUCTION

Adverse drug reactions (ADRs) are types of adverse drug events (ADEs) (1). ADEs include ADRs, medication errors, and other drug-related problems. ADEs are the negative consequences of drug misadventures. Henri Manasse defined drug misadventure as the iatrogenic hazard that is an inherent risk when drug therapy is indicated. This chapter will focus on ADRs.

DEFINITIONS

The World Health Organization's (WHO) and Karch and Lasagna's definitions of an ADR are quite similar. An ADR is any response to a drug that is noxious and unintended, and occurs at doses used for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose (2). The Food and Drug Administration (FDA) focuses on ADRs that have unexpected reactions and/or those of more significant morbidity. These ADRs would include those where the patient outcome is death, life-threatening, hospitalization, disability, congenital anomaly, or required intervention to prevent permanent impairment or damage (3). The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is concerned with the reporting of significant ADRs. Those that result in morbidity, require additional treatment, require an increased length of stay, temporarily or permanently cause disability, or cause death must be reported to the FDA (4). The American Society of Health-System Pharmacists (ASHP) defines significant ADRs as any unexpected, unintended, undesired, or excessive response to a drug that includes the following:

- Requires discontinuing the drug
- Requires changing the drug therapy
- Requires modifying the dose
- Necessitates admission to the hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis or results in temporary or permanent harm, disability, or death (5)

The ASHP definition does not include reactions due to drug withdrawal, drug abuse, poisoning, or drug complications.

Other terms that may be included as ADRs are side effects, drug intolerance, idiosyncratic reactions, toxic reactions, allergic reactions, or hypersensitivity reactions (6). *Side effects* are reactions that are unintended and unwanted but are known pharmacologic effects of the drug and occur with predictable frequency. *Drug intolerance* is a mild reaction to a drug that results in little or no change in patient management. *Idiosyncratic reaction* is an unexpected response that occurs with usual dose of a drug. *Toxic reaction* is a predictable response that results from greater than recommended drug dosages or drug concentration in the body. *Allergic or hypersensitivity reaction* is an unusual sensitivity to a drug of an immunologic nature.

CLASSIFICATION SYSTEMS

Four classification systems are used to describe ADRs (1, 7). ADRs can be classified according to the pharmacologic effect of the drug—Type A, B, C, and D reactions. Type A reactions are exaggerated but normal pharmacologic actions of a drug. They are predictable and dose dependent. Type B reactions are not predictable given the known pharmacologic action of a drug and are not dose related. Many of these Type B reactions are hypersensitivity or immune-based. These reactions can be further subdivided into type I (IgE-mediated reaction), II (IgG or IgM-mediated cytotoxic reaction), III (IgG-mediated immune complex reactions), and IV (cell-mediated immune reaction). Type C reactions are those due to long-term use of a drug. Type D reactions are delayed drug effects, such as due to carcinogenicity or teratogenicity.

ADRs can also be classified according to the dose relationship, i.e., dose-related and non-dose-related reactions. Another classification system is based on the causal relationship between the reaction and the drug. One of the

most widely used causality classifications is based on Naranjo's descriptions. These categories include definite (drug is likely the true cause), probable (drug is the apparent cause), possible (drug appears to be associated), and remote (drug is not likely to be the cause). The fourth classification system is based on degree of injury or severity of reaction. There are mild reactions (temporary discomfort and tolerable), moderate (significant discomfort), and severe (potentially life threatening or causing permanent disability or death).

INCIDENCE

The frequency of ADRs in the general population is unknown. However, the reported rates of new occurrences for ADRs are noted for selected patient populations. A meta-analysis of 39 prospective studies reported an overall incidence of serious ADRs in hospitalized patients of 6.7% and of fatal ADRs of 0.32% (8). The fatality rate makes ADRs the fourth to sixth leading cause of death in the United States. Another meta-analysis of 36 studies indicated that approximately 5% of hospital admissions are due to ADRs (9). The costs of ADRs are estimated to be $1.56–$4 billion in direct hospital costs per year in the United States (10).

FACTORS PREDISPOSING TO ADRS

Two major factors predispose to adverse drug reactions: the drug itself and patient factors. Factors related to the drug include its dose, dosage form and delivery system, and interactions between drugs. Patient-related factors include age, disease states, genetics, gender, nutrition, multidrug therapy use, and use of herbal therapies.

Drug-Related Factors

Dose

ADRs may be the result of ingestion of increased amounts of a drug. Dosing issues are especially likely with narrow therapeutic index drugs. Examples of these types of drugs include digoxin, anticoagulants, anticonvulsants, antiarrhythmics, antineoplastic agents, bronchodilators, sedatives, and hypnotics (11).

Dosage form and delivery system

Many of the ADRs related to the dosage form and delivery system are the result of local irritation or hypersensitivity reactions (12). Local irritation to the gastrointestinal (GI) tract can occur with oral dosages. For example, toxicity resulting in mouth ulcerations is associated with antineoplastic drugs. In addition, the use of certain formulations, such as sustained release preparations, can increase esophageal injury if esophageal transit is delayed. For example, a controlled release wax matrix of potassium chloride has been associated with significant esophageal erosions. Factors identified to predispose to esophageal injury include large film-coated tablets, capsules, large sustained-release preparations, rapidly dissolving formulations, and ingestion of solid oral dosage forms before bed rest with very little water intake (12).

Localized tissue irritation can be seen from the intramuscular (IM) route. This is especially an issue when the formulation pH differs from the pH of the surrounding tissue or when precipitation of poorly soluble drugs occurs (12). Incorrect administration of IM injections is probably the most important factor that causes local adverse effects. Local skin irritation can also be seen with transdermal delivery systems due to the alcohols, nonionic surfactants, and adhesives.

Hypersensitivity reactions can occur due to the presence of contaminants or excipients in pharmaceutical dosage forms (e.g., outbreaks of eosinophilia-myalgia syndrome associated with oral tryptophan contaminants in various drugs) (12). Another example is the anaphylactoid reactions to the surfactant Cremaophor EL, which is used in paclitaxel (Taxol).

Direct toxicity effects related to use of preservatives also has been documented. For example, severe metabolic acidosis and death in infants was attributed to the presence of benzyl alcohol, a preservative used in bacterostatic normal saline that was used to flush catheters (12).

The use of specific intravenous (IV) delivery devices also can cause ADRs. For instance, use of plastic infusion sets for IV administration of nitroglycerin has resulted in subtherapeutic effects due to diffusion of the drug into the plastic tubes (12).

Formulation effects, such as bioavailability differences, can cause ADRs when patients are switched to generic products. For example, significant adverse effects have occurred with anticonvulsants and thyroid preparations (12).

Interactions between drugs

It has been estimated that 6.9% of ADRs are due to drug–drug interactions (6). The most likely reason for an adverse drug interaction is the pharmacokinetic changes that result in altered metabolism or excretion of drugs, or the

pharmacodynamic changes that result in synergistic or additive effects of drugs.

Patient-Related Factors

Age, disease states, genetics, gender, nutrition, multidrug therapy use, and herbal therapies use are patient-related factors that influence the likelihood of adverse drug reactions.

Age—geriatrics

Age-related alterations in pharmacokinetics and pharmacodynamics may affect the response of elderly patients to certain medications, and may increase the susceptibility for ADRs among elderly patients (13–15) (Table 1). The risk of ADRs among elderly patients is probably not due to age alone. ADRs may be related more to the degree of frailty and medical conditions of the patient (15). On average, older persons have five or more coexisting diseases that may increase the risk of adverse events. Polypharmacy seems to be more of a common problem among the elderly. The average elderly patient takes 4.5 chronic medications and fills 13 prescriptions yearly (15). Elderly patients appear to have a decline in homeostatic mechanisms. The imbalance of homeostatic mechanisms and the decline in function reserves may put a patient at greater risk for ADEs due to decreased tolerance of medications and the ability to handle stressful situations (16).

Age—pediatrics

The two factors responsible for increasing risks of ADRs in children are pharmacokinetic changes and dose delivery issues. Age-related differences in pharmacokinetics in children are documented (17). However, the data on both efficacy and safety are often limited or not studied at all in this population. Thus, it is unclear whether an increased risk for ADRs exists in this group. However, there is a potential risk for increased ADRs if appropriate considerations are not taken into account in view of pharmacokinetic changes (18).

It is important to note that only one-fourth of the drugs approved by the FDA have indications specific for use in a pediatric population (17). Medications used in adults are often given to children without FDA safety and efficacy data. Compatibility and stability issues with dosage forms intended for adults that have been altered (e.g., dilution or reformulation) can increase risks for ADRs.

Information on pediatric age-related difference in neonates, children, and adolescents may aid in prevention of pediatric ADRs (18) (Table 2). Further studies of drug use in pediatrics are needed in order to prevent ADRs.

Concurrent diseases

Diseases such as hepatic or renal diseases can influence the incidence of ADRs by altering the pharmacokinetics of drugs, such as absorption, distribution, metabolism, or excretion (6).

Hepatic disease

Patients with liver disease have an increased susceptibility to certain drugs due to decreased hepatic clearance for drugs metabolized by the liver or due to enhanced sensitivity (6). For example, impaired hepatic metabolism can precipitate central nervous system (CNS) toxicity in patients on theophylline, phenytoin, or lidocaine; or ergot poisoning on ergotamine (19).

Increased sensitivity to drugs is also encountered in liver disease(19). The use of anticoagulants increases the risk of bleeding due to the reduced absorption of vitamin K or decreased production of vitamin K-dependent clotting factors. There is an enhanced risk for respiratory depression and hepatic encephalopathy due to morphine

Table 1 Geriatric age-related changes in pharmacokinetics

Pharmacokinetic phase	Pharmacokinetic parameters
Gastrointestinal absorption	Unchanged passive diffusion and no change in bioavailability for most drugs
	↓ Active transport and ↑ bioavailability for some drugs
	↓ First-pass effect and ↑ bioavailability
Distribution	↓ Volume of distribution and ↑ concentration of water soluble drugs
	↑ Volume of distribution and ↑ half-life for fat soluble drugs
	↑ or ↓ free fraction of highly plasma protein-bound drugs
	↓ Clearance and ↑ half-life for some Phase I
Oxidation drugs	↓ Clearance and ↑ half-life of drugs with high extraction ratio
Renal excretion	↓ Clearance and ↑ half-life of renally eliminated drugs

↓ = Decreased; ↑ = Increased.

Table 2 Pediatric age-related risk factors and causes of ADRs

Neonates:
Placental transfer of drug before birth
Differing drug action
Altered pharmacokinetics
Increased percutaneous absorption
Decreased renal/hepatic function
Decreased plasma protein binding
Use of multiple drugs
Limited information on drug action in critically ill and premature neonates
Children:
Paradoxical effect of medications (excitability rather than sedation from antihistamines)
Excipients of liquid dosage forms
Sugar as sweeteners
Propylene glycol as solvent
Large volume intravenous solutions
Treatment of viral infections with antibiotics
Disruption of neurologic and somatic development
Adolescents:
Autonomy seeking
Use and misuse of devices (e.g., tampons)
Use and misuse of prescription and nonprescription medications
Poor compliance with instructions
Use of multiple medications
Recreational use of alcohol and illicit drugs
Effects of changing hormone levels on drugs

(From Ref. 7.)

or barbiturates in patients with severe liver disease. Vigorous use of diuretics can precipitate hepatic coma due to potassium loss in liver disease. There is an increased risk of hypoglycemia with sulphonylurea antidiabetic drugs due to decreased glycogenesis in liver disease.

Liver disease can also cause hypoalbuminemia due to decreased liver synthesis of albumin. For drugs that are extensively bound to albumin, such as phenytoin, an enhanced risk of drug toxicity could occur because of the increase in free drug concentration.

There are no useful methods to quantify the degree of liver disease that can assist in dosage adjustment. A practical approach involves checking patients for elevated prothrombin time, rising bilirubin levels, and/or falling albumin levels. In such instances, drugs that have an altered response in liver disease or cause hepatotoxicity need to be avoided.

Renal disease

Impaired renal function increases the incidence of ADRs for drugs that depend on the kidney for their elimination. Unlike liver disease, use of pharmacokinetic dosing principles can minimize the risk for adverse effects.

Mechanisms responsible for enhanced ADRs in renal disease include delayed drug excretion, decreased protein binding due to hypoalbuminemia, and increased drug sensitivity (6). Delayed renal excretion is responsible for enhanced toxicity with drugs such as aminoglycosides, digoxin, vancomycin, chlorpropamide, H2-antagonists, allopurinol, lithium, insulin, and methotrexate (20). For some drugs, the accumulation of a toxic metabolite during renal failure is responsible for ADRs. This is the case with meperidine, where a toxic metabolite, normeperidine, accumulates in renal failure (20).

Patients with accumulation of uremic toxins have increased sensitivity to certain drugs. There may be an enhanced response to CNS depressants (such as barbiturates and benzodiazepines), hemorrhagic effects from aspirin or warfarin, and other bleeding effects from antibiotics that inhibit platelet aggregation, such as carbenicillin, ticarcillin, and piperacillin.

Other diseases

On theoretical grounds, other diseases associated with hypoalbuminemia could predispose patients to adverse reactions and to altered responses to drugs that are highly protein bound (21) (Table 3).

The presence of other diseases can influence the risk for ADRs. Many of these adverse effects are related to an extension of the pharmacologic effects of the drug in the presence of certain pathophysiology. Numerous examples are given in Table 4 (6).

Patients who have had a previous reaction to drugs are also more likely to experience an ADR (22). Patients with history of allergic diseases also have an increased risk due to a genetically related ability to form immunoglobulin E.

Genetic factors

Genetic factors account for some ADRs due to either altered pharmacokinetics or by altering tissue responsiveness. Altered metabolism of drugs occurs due to

Table 3 Conditions associated with hypoalbuminemia

Aging	Liver disease
Burns	Nephrotic syndrome
Cancer	Nutritional deficiency
Cardiac failure	Pregnancy
Protein-losing enteropathy	Renal failure
Inflammatory diseases	Sepsis
Injury	Stress
Immobilization	Surgery

Table 4 Influence of diseases on adverse drug reactions

Disease	Drug	Adverse reactions
Gastrointestinal		
Peptic ulcer	Aspirin, corticosteroids, nonsteroidal antiinflammatory drugs	Risk of bleeding or perforation of ulcer
Cardiovascular		
Heart failure	β-Blockers	Aggravate or precipitate heart failure
	Lidocaine, theophylline	Enhanced toxicity—seizures
Myocardial ischemia	Tricyclic antidepressants	Disturbances of cardiac rate, rhythm, and conduction
	Digoxin	Arrhythmias
Bradycardia	β-Blockers	Cardiac standstill
	Quinidine	
Hypertension	Oral contraceptives, vasoconstrictors	Increased blood pressure
	Phenothiazines, nitrates	Decreased blood pressure
	Tricyclic antidepressants	
Hematologic		
Bleeding disorders—hemophilia	Aspirin	Increased risk of hemorrhage
Neurological disorders		
Myasthenia gravis	Aminoglycosides	Aggravate muscle weakness
	Quinidine, quinine	Paralysis
Epilepsy	Phenothiazines	Lower seizure threshold
	Tricyclic antidepressants	
Cerebrovascular	Ergotamine	Ischemic episodes
Rheumatic		
Systemic lupus	Drugs	Increased incidence of drug reactions in general
Hyperuricemia	Thiazide diuretics, furosemide	Gouty attack
Respiratory		
Asthma	β-Blockers	Acute bronchospasms
Respiratory insufficiency	Narcotic analgesics	Hypoventilation, respiratory arrest
Endocrine disorders		
Diabetes mellitus	Thiazide diuretics, furosemide, corticosteroids, oral contraceptives	Hyperglycemia; aggravates diabetic control
Hypothyroidism	Digoxin	Enhanced response
Hyperthyroidism	Oral anticoagulants	Enhanced response
	Digoxin	Decreased response
Ocular		
Narrow-angle glaucoma	Anticholinergics	Glaucoma attack

differences in hydrolysis, acetylation, and hepatic oxidation of drugs. Altered pharmacodynamic reactions could be either an exaggerated response or a qualitative response. These types of reactions are unpredictable. Examples of altered drug response due to genetic factors are found in Table 5 (6).

Gender

A higher incidence of ADRs has been reported for women in comparison to men (6). One reason for this observation is that women take more drugs than men. Yet, no sex-linked differences in drug pharmacokinetics have been documented. Other reports have not supported a higher incidence of ADRs in women as compared to men. Thus, sex alone is unlikely to be a major determinant of ADRs.

Nutrition

Nutritional factors are also responsible for ADRs. These factors include the interaction of drugs and nutrients, and altered pharmacokinetics related to nutritional status.

One study reported a very low incidence (0.4%) of clinically significant drug–nutrient interactions in a teaching hospital (23). Three mechanisms postulated for drug–nutrient interactions are interference with drug absorption, alteration of drug excretion, and affecting drug activity. For example, the absorption of tetracycline is reduced by chelation with iron, calcium, and magnesium. Foods that acidify or alkalinize the urine can affect drug excretion. Foods that contain a large amount of vitamin K can inhibit the activity of warfarin. A listing of important drug–nutrient interactions is found in Table 6 (23). A review article on drug–food interactions in clinical practice is found in Ref. 24.

Drug–nutrient interactions may be more highly significant in renal failure patients. A review article of drug–nutrient interactions in renal failure has been published (25).

Nutritional status can affect drug pharmacokinetics. Malnutrition states can cause the following: 1) the liver and kidneys changes affect drug elimination; 2) GI system changes affect drug absorption; 3) changes in the heart affect blood flow; 4) hormone changes affect metabolic enzymes and drug binding proteins; 5) plasma, tissue proteins, and body composition changes affect protein binding and elimination; 6) mineral and electrolyte changes affect drug metabolism and protein binding; and 7) tissue changes affect uptake of drugs and drug–receptor interactions (26).

Multidrug use

According to several epidemiological studies, multiple drug use has a strong association in the causality of ADRs. It has been suggested that the more medications used, the higher the risk for ADRs (27). Consistent drug regimen reviews by healthcare providers in order to reduce polypharmacy may decrease the risk of ADRs.

Herbal therapies use

The use of herbal therapies increased dramatically during the 1990s. Herbal therapy sales are estimated to be $4 billion a year, with sales increasing at 20% per year since the early 1990s (28). Patients often mistakenly believe that since these products are natural, they do not possess the potential harm as in prescription medications. Since herbal medications are sold and marketed without stringent FDA approval and guidelines, limited evidence-based data on efficacy, adverse effects, and drug interactions exist. Recently, two review articles examined available data on ADRs for the most common herbal medications (28, 29). Many of these available reports fall short on documentation of temporal relationship with the specific ADR and the herbal drug.

For most conditions, herbal products are not a replacement for proven prescription or nonprescription drugs. Patients should be aware that health care practitioners cannot guarantee the safety and consistency of herbal products. Patients should start with the recommended effective doses and report any unusual side effects to their health care practitioner. Patients should always consult with their pharmacist for possible drug–herbal interactions. Side effects and possible drug interactions for the ten most commonly used herbals are listed in Table 7.

ADVERSE DRUG REACTION REPORTING SYSTEMS

The WHO, the FDA, the JCAHO, and the Health Care Financing Administration (HCFA) have all addressed and mandated the need for health care institutions to implement an ADE detection and reporting system. Detection systems are instrumental in postmarketing surveillance of ADRs. The JCAHO requires all accredited health care institutions to have an ongoing drug surveillance program (4). The goals of ADR detecting and reporting systems are to aid in postmarketing surveillance of FDA approved medications and to identify ways to decrease ADR risks. The main focus of all of these reporting systems is to aid in promoting improvements in the medication use process.

Table 5 Genetic factors and altered drug responses

Genetic mechanism	Drug(s)	Adverse drug response
Pharmacokinetic		
Low plasma pseudocholinesterase	Succinylcholine	Prolonged neuromuscular blockade leading to apnea
Slow acetylator	Isoniazid	Increased incidence of peripheral neuropathy; SLE-like syndrome; and more prone to phenytoin toxicity
	Hydralazine, procainamide	Increased incidence of SLE-like syndrome
	Phenelzine, sulfasalazine	More prone to side effects
Rapid acetylator	Isoniazid	More prone to hepatitis
Deficiency of epoxide hydrolase	Phenytoin, carbamazepine, phenobarbital	Life threatening hypersensitivity syndrome due to accumulation of toxic intermediates
Pharmacodynamic		
Glucose 6-phosphate dehydrogenase deficiency (G-6-PD)	Aspirin, BAL (dimercaprol), chloroquine, chloramphenicol, dapsone hydroxychloroquine, nalidixic acid, nitrofurantoin, primaquine, probenecid, quinine, quinidine, sulfonamides	Hemolytic anemia
Methemoglobin reductase deficiency	Acetaminophen, anesthetics, topical, benzocaine, chloroquine, dapsone, nitrites, primaquine, sulfonamides	Methemoglobinemia
Abnormality of calcium regulation	Anesthetics, general, (halothane), muscle relaxants (succinylcholine)	Malignant hyperpyrexia

Table 6 Important drug-nutrient interactions

Drug	Nutrient	Interaction
Phenytoin	Alcohol	Enhanced metabolism of phenytoin
	Enteral feedings	Decreased phenytoin absorption
Tetracycline	Dairy products	Impaired drug absorption
Theophylline	Caffeine	Potential for toxic effects
Warfarin	Foods high in vitamin K	Decreases anticoagulant response
Chlorpropamide, tolbutamide, tolazamide, acetohexamide, metronidazole	Alcohol	Disulfiram-like reaction
Trancylcypromide	Foods high in tyramine	Hypertensive crisis
Disulfiram	Alcohol	Nausea, blurred vision, chest pain, dizziness, fainting
Spironolactone	Foods high in potassium	Hyperkalemia

(Adapted from Ref. 23.)

ADR Screening Methods

The best methodology for screening for ADRs has not been determined. However, several screening methods have been proposed. In particular, the literature has highlighted five screening methods using clinical data (30–34). The five include screening for: 1) "tracer drugs," e.g., antidotes such as vitamin K and diphenhydramine; 2) "narrow therapeutic range drugs," e.g., follow-up of computer lab values for warfarin and digoxin; 3) change in medications, e.g., documentation of discontinued medications or decreased dose; 4) diagnosed ADRs documented in the medical record, e.g., chart review or reviewing ICD-9 CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes; and 5) ADR computer report tracking systems. Although each of these ADR screening methods has been described in detail, limited data are available on the productivity of these screens.

Systems for Pharmaco-epidemiologic Studies

Pharmacoepidemiology is used to detect ADRs (35, 36). Several types of systems use pharmacoepidemiologic methods. These include spontaneous reporting, studies of therapeutic classes, and studies of specific medical syndromes.

Spontaneous reporting

Spontaneous reporting is currently the major backbone for the detection of ADRs (37). It occurs in one of three ways:

1. Reporting to the FDA as part of clinical trials;
2. Reporting by practitioners to medical journals; or
3. Patients' self-reporting to either manufacturers or the FDA (38).

Clinical trials in new drug development cannot detect all the possibilities for drug safety. Limitations in Phase III clinical trials include a relatively small sample size, short duration of the trial, restricted populations (e.g., geriatrics and pediatrics), uncomplicated patients, (e.g., limited disease states), and limited power for adverse drug reaction detection (30). Thus, the FDA relies heavily on spontaneous reporting of suspected ADRs (39). Spontaneous reporting is important in early market history of the drug to determine previously unidentified drug reactions. This has been particularly true in the last few years because of numerous new medications that have entered the market and now carry a black box warning. For example, Rezulin® and Trovan® are associated with hepatotoxicity and carry black box warnings.

Additional advantages of spontaneous reporting systems include the detection of extremely rare ADRs and ability to identify at-risk subgroups. In order to enhance the spontaneous reporting system approach, the FDA developed the MedWatch form. This form can be faxed to the agency (1-800-FDA-1078) or called in (1-800-FDA-1088) (40). The forms also can be obtained by the "MedWatch Online" internet-based website (http://www.fda.gov/medwatch/).

Limitations of FDA spontaneous reporting include both under-reporting and over-reporting.

An example of over-reporting occurs with recently approved drugs. This is partly due to enhanced publicity about these drugs.

Table 7 ADRs for the top ten herbal medicines

Herbal	Common use	Side effects and interactions
Echinacea	Treatment and prevention of upper respiratory infections, common cold	Rash, pruritis, dizziness, unclear long-term effects on the immune system.
St. John's wort	Mild to moderate depression	Gastrointestinal upset, photo-sensitivity. Mild serotonin syndrome with the following medications: paroxetine, trazodone, sertraline, and nefazodone. May decrease digoxin levels. May decrease cyclosporine serum concentrations. Combined oral contraceptives—breakthrough bleeding.
Gingko biloba	Dementia	Mild gastrointestinal distress, headache, may affect warfarin (increase INR). Interaction with aspirin (spontaneous hyphema)
Garlic	Hypertension, hypercholesterolemia	Gastrointestinal upset, gas, reflux, nausea, allergic reactions, and antiplatelet effects. May effect warfarin (increase INR)
Saw palmetto	Benign prostatic hyperplasia	Uncommon
Ginseng	General health promotion, sexual function, athletic ability, energy, fertility	High doses may cause diarrhea, hypertension, insomnia, nervousness, may affect warfarin (decreased INR)
Goldenseal	Upper respiratory infections, common cold	Diarrhea, hypertension, vasoconstriction
Aloe	Topical application for dermatitis, herpes, wound healing, and psoriasis, orally for constipation	May delay wound healing after topical application. Diarrhea, and hypokalemia with oral use
Siberian ginseng	Similar to ginseng	May raise digoxin levels. May affect warfarin (increased INR)
Valerian	Insomnia, anxiety	Fatigue, tremor, headache, paradoxical insomnia (not advised with other sedative-hypnotics)

Studies of therapeutic classes

Observational cohort or case control designs have been used to determine ADR relationships with specific therapeutic classes (36, 41). Medical claims data are often used in these studies and caution should be warranted due to lack of definite confirmation of drug exposure and the potential for confounding variables (38). However, these studies have been beneficial in determining risk of ADRs with specific classes (e.g., NSAIDs and the risk of peptic ulcer disease) (42).

Studies of specific medical syndromes

Observational cohort or case control designs can also be useful to study possible causality relationships of specific medical conditions or syndromes due to drug exposure (36, 41). These types of studies have been particularly useful in examining ADRs in a specific population, such as geriatric or pediatric patients. These groups of patients are often excluded in Phase III trials. However, a disadvantage of these studies is that they also often use administrative data. These data can warrant risk of problems in determining causality due to potential confounding variables (38).

Assessing Adverse Drug Reactions

After detection of a possible ADE, causality assessment needs to be performed. It is important to be able to rank the likelihood of an ADR as unlikely, possible, probable, or definite. A major problem with determining causality is that confounding variables can contribute to the complexity of causality assessment (43). In order to determine causality, several important points of data are required. These include the nature of the adverse event, name of the putative drug, other potential causes, and the temporal relationship

Table 8 ADR Naranjo causality algorithm

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes (other than drug) that could on their own caused this reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

Probability category scores: Definite ≥ 9; Probable 5–8; Possible 1–4; Doubtful ≤ 0.

between the drug and adverse event. Potential causes are obtained by examining the medical history, physical examination findings, and directed diagnostic tests.

Identification of causality can be performed simply by using a health care provider's clinical reasoning and judgment. The main disadvantage to this approach is a low inter-rater and intra-rater agreement for ADR causality (44, 45).

An ADR causality algorithm addresses the issue of inter-rater and intra-rater reliability with a series of clinical questions. For example, the Naranjo algorithm consists of a series of clinical questions that focus on temporal and dose–response relationships, consistency of the ADR with previous clinical reports or patient experiences, placebo response, drug dechallenge and rechallenge, toxic blood drug concentrations, alternative causes of the reaction, and whether the event was confirmed by objective evidence (44) (Table 8). Numerous health care institutions and the FDA use some type of causality algorithm to minimize disagreement among different evaluators and improve inter-rater and intra-rate agreement.

PREVENTING ADVERSE DRUG REACTIONS

ADRs are problematic in that they cause significant morbidity and mortality. Almost 95% of ADRs are Type A (predictable) reactions, and thus with quality improvement measures, ADRs can be avoided and prevented (46). Knowledge of causative factors and an increase in patient education may help prevent ADRs. Improvements in the documentation of allergic reactions (e.g., via computer tracking), development of tools to enhance compliance, and application of tools to improve prescribing and administration of drugs are other preventative approaches to ADRs.

In 1994, the ASHP, the American Medical Association (AMA), and the American Nurses Association (ANA) generated the following system of recommendations to prevent ADRs in health care systems:

1. Health care systems should establish processes in which prescribers enter medication orders directly into computer systems.
2. Health care systems should evaluate the use of machine-readable coding (e.g., bar coding) in their medication use processes.
3. Health care systems should develop better systems for monitoring and reporting adverse drug events.
4. Health care systems should use unit dose medication distribution and pharmacy-based intravenous medication admixture systems.
5. Health care systems should assign pharmacists to work in patient care areas in direct collaboration with prescribers and those administering medications.

6. Health care systems should approach medication errors as system failures and seek system solutions in preventing them.
7. Health care systems should ensure that medication orders are routinely reviewed by the pharmacist before first doses and should ensure that prescribers, pharmacists, nurses, and other workers seek resolution whenever there is any question of safety with respect to medication use (47).

SUMMARY

Adverse drug reactions are of significant concern in the pharmaceutical technology arena. Various drug and patient factors that predispose to ADRs have been identified. Reporting systems used to screen and assess ADRs facilitate the understanding of risk factors and contribute to the development of systematic improvement in the prevention of ADRs.

REFERENCES

1. Schumock, G.; Guenette, A. Adverse Drug Events. *Pharmacotherapy Self-Assessment Program*; Carter, B., Ed.; ACCP: Kansas City, MO, l999; 5, 103–130.
2. Karch, F.E.; Lasagna, L. Adverse Drug Reactions: A Critical Review. JAMA **l975**, *234*, 1236–1241.
3. Rossi, A.; Knapp, D. Discovery of New Adverse Drug Reactions. A Review of the Food and Drug Administration's Spontaneous Reporting System. JAMA **1984**, *252*, 1030–1033.
4. *Joint Commission on Accreditation of Health Care Organizations. l998 Comprehensive Accreditation Manual for Hospitals*; A.M.H: Oakbrook Terrace, IL, 1997.
5. American Society of Health-System Pharmacists. Suggested Definitions and Relationships Among Medication Misadventures, Medication Errors, Adverse Drug Events and Adverse Drug Reactions. Am. J. Health-Syst. Pharm. **1998**, *55*, 165–166.
6. Edwards, I.R. Pharmacological Basis of Adverse Drug Reactions. *Avery's Drug Treatment*; Speight, T., Holford, N., Eds.; ADIS International LTD: Auckland, New Zealand, 1997; 261–299.
7. Young, L.R.; Wurtzbacher, J.D.; Blankenship, C.S. Adverse Drug Reactions: A Review for Healthcare Practitioners. Am. J. Managed Care **1997**, *12*, 1884–1906.
8. Lazarou, J.; Pomeranz, B.; Corey, P. Incidence of Adverse Drug Reactions in Hospitalized Patients. JAMA **1998**, *279* (15), 1200–1205.
9. Einarson, T. Drug-Related Hospital Admissions. Ann. Pharmacother. **1993**, *27*, 832–840.
10. Clasen, D.C.; Pestonik, S.L.; Evans, R.S.; Lloyd, J.F.; Burke, J.P. Adverse Drug Events in Hospitalized Patients: Excess Length of Stay, Extra Costs, and Attributable Mortality. JAMA **1997**, *277*, 301–306.
11. *Applied Biopharmaceutics and Pharmacokinetics*; Shargel, L., Yu, A., Eds.; Appleton and Lange: Stamford, CT, 1999.
12. Uchegbu, I.; Florence, A. Adverse Drug Events Related to Dosage Forms and Delivery Systems. Drug Safety Concepts **1996**, *14* (1), 39–67.
13. Swift, C.G. Pharmacodynamics: Changes in Homeostatic Mechanisms, Receptor and Target Organ Sensitivity in the Elderly. Br. Med. Bull. **1990**, *46*, 36–52.
14. Parker, B.M.; Cusack, B.J.; Vestal, R.E. Pharmacokinetic Optimisation of Drug Therapy in Elderly Patients. Drugs Aging **1995**, *7*, 10–18.
15. Gurwitz, J.H.; Avorn, J. The Ambiguous Relation Between Aging and Adverse Drug Reactions. Ann. Intern. Med. **1991**, *114*, 956–966.
16. Taffet, G.E. Age-Related Physiologic Changes. *Geriatric Review Syllabus: A Core Curriculum in Geriatric Medicine*; Reuben, D.B., Yoshikawa, T.T., Besdine, R.W., Eds.; Kendall/Hunt for the American Geriatric Society: Dubuque, IA, 1996; 11–24.
17. Nahata, M.C. Pediatrics. *Pharmacotherapy A Pathophysiologic Approach*; DiPiro, J.T., Talbert, R., Yee, G.C., Matzke, G.R., Wells, B.G., Posey, M.L., Eds.; Appleton & Lange: Stanford, CT, 1999; 44–51.
18. Gupta, A.; Waldhauser, L.K. Adverse Drug Reactions from Birth to Early Childhood. Pediatr. Clin. North. Am. **1997**, *44*, 79–92.
19. Piper, D.W.; deCarle, D.J.; Talley, N.J.; Gallagher, N.D.; Wilson, J.S.; Powell, L.W.; Crawford, D.; Gibson, P.R.; Sorrell, T.C.; Kellow, J.E.; Roberts, R.K. Gastrointestinal and Hepatic Diseases. *Avery's Drug Treatment*; Speight, T., Holford, N., Eds.; ADIS International LTD: Auckland, New Zealand, 1997; 1010–1012.
20. Critchley, J.A.; Chan, T.Y.K.; Cumming, A.D. Renal Diseases. *Avery's Drug Treatment*; Speight, T., Holford, N., Eds.; ADIS International LTD: Auckland, New Zealand, 1997; 1107–1109.
21. Tillement, J.P.; Lhoste, F.; Giudicelli, J.F. Diseases and Drug Protein Binding. Clin. Pharmacokinet **1978**, *3*, 144–154.
22. Smith, J.W.; Seidl, L.G.; Cluff, L.E. Studies on the Epidemiology and Adverse Drug Reactions. Ann. Intern. Med. **1966**, *65*, 629–640.
23. Franse, V.; Stark, N.; Powers, T. Drug-Nutrient Interactions in a Veterans Administration Medical Center Teaching Hospital. Nutrition in Clinical Practice **1988**, *3* (4), 145–147.
24. Yamreudeewong, W.; Henann, N.; Fazio, A.; Lower, D.; Cassidy, T. Drug-Food Interactions in Clinical Practice. J. Fam. Pract. **1995**, *40* (4), 376–384.
25. Mason, N.; Boyd, S. Drug-Nutrient Interactions in Renal Failure. J. Renal Nutrition **1995**, *5* (4), 214–222.
26. Krishnaswamy, K. Drug Metabolism and Pharmacokinetics in Malnutrition. Clin. Pharmacokinet **1978**, *3*, 216–240.
27. Grymonpre, R.E.; Mitenko, P.A.; Sitar, D.S.; Aoki, F.Y.; Montgomery, P.R. Drug-Associated Hospital Admissions in Older Medical Patients. J. Am. Geriatr. Soc. **1988**, *36*, 1092–1098.

28. Mar, C.; Bent, S. An Evidence-Based Review of the 10 Most Commonly Used Herbs. West. J. Med. **1999**, *171*, 168–171.
29. Fugh-Berman, A. Herb-Drug Interactions. Lancet **2000**, *355*, 134–38.
30. American Society of Health-System Pharmacists. ASHP Guidelines on Adverse Drug Reaction Monitoring and Reporting. Am. J. Health-Syst. Pharm. **1995**, *52*, 417–419.
31. Johnston, P.E.; Morrow, J.D.; Branch, R. Use of a Database Computer Program to Identify Trends in Reporting Adverse Drug Reactions. Am. J. Hosp. Pharm. **1990**, *47*, 1321–1327.
32. Koch, K.E. Use of Standard Screening Procedures to Identify Adverse Drug Reactions. Am. J. Hosp. Pharm. **1990**, *47*, 1314–1320.
33. O'Neil, A.C.; Petersen, L.A.; Cook, E.F.; Bates, D.Q.; Lee, T.H.; Berman, T.A. Physician Reporting Compared With Medical-record Review to Identify Adverse Medical Events. Ann. Intern. Med. **1993**, *119*, 370–376.
34. Prosser, T.R.; Kamysz, P.L. Multidisciplinary Adverse Drug Reaction Surveillance Program. Am. J. Hosp. Pharm. **1990**, *47*, 1334–1339.
35. Porta, M.S.; Hartzema, A.G. The Contribution of Epidemiology to the Study of Drugs. Drug. Intell. Clin. Pharm. **1987**, *21*, 41–47.
36. Strom, B.L., Ed. *Pharmacoepidemiology*, 2nd Ed.; John Wiley: Chichester, 1994.
37. *The Detection of New Adverse Drug Reactions*; Stephens, M.D.B., Ed.; The MacMillan Press: Basingstoke, 1988.
38. Hanlon, J.T.; Schmader, K.; Lewis, I. Adverse Drug Reactions. *Therapeutics in the Elderly*; Delafuente, J.C., Stewart, R.B., Eds.; Harvey Whitney Books: Cincinnati, 1995; 212–227.
39. Kennedy, D.L.; McGinnis, T. Monitoring Adverse Rrug Reactions: The FDA's New MedWatch Program. Pharmacol. Ther. **1993**, *833–834*, 839–842.
40. Kessler, D.A. Introducing MEDWatch: New Approach to Reporting Medication and Device Adverse Effects and Product Problems. J.A.M.A. **1993**, *269*, 2765–2768.
41. *Pharmacoepidemiology: An Introduction*; Hartzema, A.G., Porta, M.S., Tilson, H.H., Eds.; Harvey Whitney Books: Cincinnati, 1991.
42. Guess, H.A.; West, R.; Strand, L.M.; Helston, D.; Lydick, E.G.; Bergman, C.A.; Wolski, K. Fatal Upper Gastrointestinal Hemorrhage of Perforation Among Users and Nonusers of Nonsteroidal Anti-Inflammatory Drugs in Saskatchewan, Canada 1983. J. Clin. Epidemiol. **1988**, *41*, 35–45.
43. Meyboom, R.H.B.; Hekster, Y.A.; Antoine, C.G.; Gribnau, F.W.J.; Edward, I.R. Causal or Casual? The Role of Causality Assessment in Pharmacovigilance. Drug Saf. **1997**, *6*, 374–389.
44. Naranjo, C.A.; Busto, U.; Sellers, E.M.; Sandor, P.; Ruiz, I.; Roberts, E.A.; Janecek, E.; Domecq, C.; Greenblatt, D.J. A Method for Estimating the Probability of Adverse Drug Reactions. Clin. Pharmacol. Ther. **1981**, *30*, 239–245.
45. Karch, F.E.; Lasagna, L. Adverse Drug Reactions: A Critical Review. JAMA **1975**, *234*, 1236–1241.
46. Rawlins, M.D. Adverse Reactions to Drugs. Br. Med. J. **1981**, *82*, 974–976.
47. American Society of Health System Pharmacists. Top-Priority Actions for Preventing Adverse Drug Events in Hospitals: "Recommendations of An Expert Panel.". Am. J. Health-Syst. Pharm. **1996**, *53*, 747–751.